REMARKS

Claim 71 has been amended as agreed at the interview, to clarify that the cores of the nanoparticles contain nothing but liquid fluorocarbon. It will be noted that the exemplified nanoparticles contain no oil, although the specification also describes particles that do. Although the specification discloses the possibility of including oil in the cores of the nanoparticles, that aspect of the invention is not being claimed. The claims are directed to the subset of nanoparticles where the cores "consist of" fluorocarbon. No new matter has been added and entry of the amendment is respectfully requested.

Applicants have received the Interview Summary mailed 7 August 2007 and agree that overall agreement was not reached and arguments with respect to Unger and Lanza were discussed. However, applicants understand that the Office intends to withdraw the rejections based on the assertion that phosphatidyl ethanolamine can be considered a drug and the rejections based on Unger. This leaves only the rejection based on inherent anticipation by Lanza. The following discussion addresses the rejections in the order they appear in the Office action mailed 18 May 2007.

Two bases for rejection were set forth in the Office action: The rejection of claims 71-79 and 82-86 as assertedly anticipated by three U.S. patents to Lanza, *et al.*, with similar disclosures as evidenced by three other cited documents and a rejection under 35 U.S.C. §§ 102/103 of claims 71-79 and 82-83 over US 2001/0018072 ('072) to Unger. These bases for rejection will be discussed in turn.

First, claims 71-79 and 82-86 were rejected as assertedly anticipated by any one of US 5,690,907 ('907), 5,780,010 ('010), or 5,958,371 ('371), all to Lanza, *et al.* The '371 is a continuation-in-part of '010, which is in turn a continuation-in-part of '907. The body of the rejection appears based on the disclosure of '907, and applicants believe that any pertinent disclosures are present in this document and that the additional subject matter in the remaining two patents is not relevant to the issues here.

There appears to be no assertion that any of the Lanza patents explicitly disclose a method to deliver a drug to a target tissue or organ by administering nanoparticles comprising a core consisting of liquid fluorocarbon coated with a lipid/surfactant layer *wherein said drug is contained in said layer and not carried or deposited in the interior of said nanoparticle*. It is evident that the Office believes that this disclosure is simply inherent in the Lanza patents.

There appear to be two bases on which the Office draws this conclusion:

1. Phosphatidyl ethanolamine (PE) is a drug and Lanza does show that this is incorporated exclusively in the lipid/surfactant layer; and

2. Other drugs would inherently and automatically reside in the lipid/surfactant layer to the exclusion of the hydrophobic core.

Applicants will address each of these in turn.

As to point 1, phosphatidyl ethanolamine is not a drug. Applicants are gratified that it appears that it was agreed at the interview that this basis for rejection was in error, and that phosphatidyl ethanolamine indeed is not a drug. However, to complete the record, the following argument is presented.

The Office asserts that PE is a drug as demonstrated by the disclosure in US 4,595,680 ('680). The Office cites the abstract of this document as describing PE as having activity against disorders related to the central nervous system. A superficial reading of the abstract might lead one to that conclusion, but the disclosure of the entire document, as was argued in the previous response to this basis for rejection, reveals that it does not have that activity. It is simply present in the composition to offset the anticoagulant activity associated with the actual drug that has activity against disorders related to the central nervous system – phosphatidylserine (PS).

This is clearly stated, for example, in column 3, beginning at line 40, which discusses the various effects of PS on the central nervous system which continues through column 3 to the beginning of column 5. A summary of what '680 discloses is the following at lines 3-11:

> In summary, pharmacological data reported in the literature make it evident that administration to man of pharmaceutical compositions containing PS of cerebral origin and with a high degree of purity may represent a valid therapeutic means for treating aging of the brain where a diminishing of dopaminergic control is well known. On the other hand, data reporting the effects of PS on blood coagulation suggests a grave risk of hemorrhage upon administration of PS.

The relevance of this statement is apparent upon reading the remainder of this patent which employs PE in admixture with PS simply to offset the anticoagulant activity of PS. As noted, at column 3, lines 16-17:

> It has been reported that PE has a marked coagulant activity.

That the function of PE is simply to offset the anticoagulant activity of PS when PS is used as a drug to treat the central nervous system is also evident, for example, in the statement in column 8, at line 45, that it has been determined that:

> A preferred phospholipid composition having good CNS activity *and without undesirable hematic coagulation effects* is obtained by preparing a mixture of from 60-75% PS with from 40-25% PE.

Indeed, claim 1 is directed to a pharmaceutical composition comprising an effective amount of phosphatidylserine where its combination with PE makes the composition "substantially free of secondary hematic coagulation effects."

This argument seems not to have been addressed in Response to Arguments.

It is also well known in the art that PE is not a drug. It is a natural component of egg yolk lecithin and cell membranes. Of course, egg yolk is used in a lot of foods, including eggs themselves. Further, egg yolk lecithins are commonly used in artificial blood products without any deleterious coagulation effects. In contrast, PS is well known to be a lipid which, when present on a cell surface, marks the cell for apoptosis through the binding of annexin-5. It has been used in lipid microbubbles to increase phagocytosis by white blood cells, such as neutrophils.

In addition to the foregoing, applicants have pointed out that phosphatidyl ethanolamine *per se* was not incorporated into the compositions of Lanza, but rather biotinylated phosphatidyl ethanolamine. There is no implication anywhere in the '680 patent that the biotinylated form of PE could be considered a drug.

This argument appears not to have been addressed in the Response to Argument, either.

In summary, the evidence of record does not show that PE is a "drug" incorporated into a lipid/surfactant layer of liquid perfluorocarbon particles as asserted by the Office.

As to point 2, applicants understand that no agreement was reached at the interview that the residence of the drug in the lipid/surfactant layer would not be inherent in the Lanza documents.

However, applicants point out that in order to ensure that a drug to be administered will reside exclusively in the lipid/surfactant layer surrounding liquid perfluorocarbon particles, it is necessary to follow a specified procedure when making the particles and adding the drug to them. The testimony of Dr. Gregory Lanza by declaration in response to the previous Office action demonstrates this. Although the Office discounts the declaration as not germane to the document cited in a different rejection, this declaration is intended, rather, to show that the drug must be mixed with the initial ingredients in a solvent such a chloroform and evaporated to a film prior to forming the nanoparticles rather than added at a later point in the preparation (see, paragraphs 2 and 3 of the Lanza Declaration).

As noted in the previous response, the Lanza, *et al.,* documents provide no instructions whatsoever as to how to prepare the particles to ensure that the drug will reside in the lipid/surfactant layer rather than be incorporated into the core or otherwise failing to associate successfully with the particles at all. Applicants in the previous response on page 11 showed the only process disclosed in Lanza for making the particles, and pointed out that there were a number of points in the process where the drug could have been added. Only if the drug is added at the very beginning is the preparation successful in assuring that the lipid/surfactant layer contains all of the drug. If added at a different stage of the preparation, the drug may not even associate with the nanoparticles.

Applicants took some pains to set forth the law on inherent anticipation citing case law which mandates that for inherency to be found, a result must be inevitable not just probable. As noted in MPEP § 2112(IV), "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" (emphasis

in the original). A number of cases are cited there that are instructive, and it should not be necessary for applicants to rehash the documentation provided in the previous response as to the requirements for inherent anticipation to be found. Quoting *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990) the MPEP in this section states that:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. (Emphasis in the original.)

Again, the law is that the inherent characteristic must always result, not just some of the time and not just maybe.

The question, then, is whether in following the procedures and descriptions set forth in Lanza, all of the drug to be administered would always reside in the lipid/surfactant layer and not in the fluorocarbon core. Clearly, the answer is no. Among the drugs listed, for example, in column 7 of Lanza '901 is 5-fluorouracil, which contains a fluoride which would be expected to have affinity for a fluorocarbon as opposed to the lipid/surfactant coating. Another well known "drug" – oxygen, preferentially resides in the fluorocarbon core. Indeed, the fluorocarbon particles themselves were first recognized as useful as a blood substitute by virtue of their oxygen-carrying capacity.

Perhaps more important, it will be noted that the exemplified nanoparticles of Lanza contain, in the emulsion and, as a portion of the core, safflower oil. It appears that the safflower oil is approximately 4% of the core itself. In view of the solubility of the drugs listed in column 7 of Lanza in oil, it is unlikely that these drugs would automatically reside exclusively in the lipid/surfactant layer, since they would be soluble in the oil contained in the core.

In contrast, the present claims have been amended to limit them to nanoparticles where the core is exclusively composed of fluorocarbon. There is no oil in these liposomes. Therefore, the liposomes used in the present invention are more suited to confining the drugs to the lipid/surfactant coating. Indeed, in most cases, drugs that are lipophilic or even hydrophilic will reside, when associated with the particles, in the lipid/surfactant layer and not reside in the core which contains no oil.

Applicants wish to emphasize that the standard for showing inherency is much higher than that for enablement. In the case of demonstrating inherency, as extensively argued previously, the "inherent" results must occur each and every time. This was dramatically illustrated in *Glaxo, Inc. v. Novopharm, Ltd.*, 52 F3d 1043, 34 USPQ2d 1565 (Fed. Cir. 1995) cert. denied 516 U.S. 988 (1995) where performing the process of an exemplified prior art document sometimes, but not always, led to the composition claimed in the invention at issue. This was insufficient for inherent anticipation. Thus, unless the nanoparticles described in Lanza '907 in combination with the drugs there described inevitably leads to the result claimed here, no inherency can be found. Clearly this is not always the case for example in view of the inclusion of oil in the cores of the exemplified Lanza nanoparticles.

Applicants believe that the foregoing addresses the concerns expressed by the Office at the interview. There are additional arguments in the Office action itself that are addressed below:

In the Office action itself, some reasoning was provided for the assertion that inherent anticipation should be found in Lanza, asserting that the present particles are equivalent to liposomes.[1]

Liposomes are familiar to those in the art, and are defined, for example, as "a microscopic spherical particle formed by a lipid bilayer enclosing an aqueous compartment." Dorland's Medical Dictionary for Health Consumers, copyright 2007 by Saunders. Or "an artificial microscopic vesicle consisting of an aqueous core enclosed in one or more phospholipid layers used to convey vaccines, drugs, enzymes or other substances to target cells or organs." (The American Heritage Stedman's Medical Dictionary, 2nd Ed., 2004, Houghton Mifflin Co.) The Office persists in insisting that the compositions of Lanza are liposomes which is clearly erroneous in the face of this definition. The particles described by Lanza have fluorocarbon cores, not aqueous cores and thus the cores are hydrophobic, not hydrophilic.

In support of equating the nanoparticles of the present invention to liposomes, the Office cites US 5,656,287 column 4, line 27. But that line says nothing about the relationship of liposomes to the particles of Lanza or the particles of the present invention. All that line says is "liposome encapsulated cyclosporin can be formulated having high entrapment characteristics with good stability." How this has anything to do with coming to the conclusion that the nanoparticles of the present invention or of Lanza are liposomes escapes applicants entirely. In response to this, the Office states that "there is no claim language indicating that the instant nanoparticles are

[1] In a way, the Office can hardly be blamed, since Example 1 in Lanza describes forming a "liposome suspension." This is clearly a regrettable, but inadvertent and obvious error.

hydrophobic," but that is not true. The claim requires that the particles have a fluorocarbon core which is hydrophobic by anybody's definition. Liposomes, of course, have aqueous cores.

The assertion of inherency is especially puzzling as the Office states on page 2 of the Office action that "it is well known in the art that a lipophilic drug will be held in a hydrophobic core and in the lipid lipophilic layer," thus supporting the position taken by applicants.

In any event, applicants now know that the drug cannot be added to the lipid surfactant after formation of the particles and successfully incorporate into the lipid/surfactant layer. The residence of the drug in the lipid/surfactant layer is, however, assured if the procedure provided in the present specification is followed, and the liposomes as presently claimed exclude the presence of oil (which could solubilize many drugs) in their fluorocarbon cores.

In summary, there appears to be no response to applicants' detailed arguments in the previous response that PE cannot be considered a drug in the context of the present application. However, it appears agreed from the discussion at the interview that PE cannot be considered a drug in this context. There has been no demonstration that the drugs listed in Lanza, if added to the nanoparticulate composition of Lanza, would inevitably and necessarily reside only in the lipid/surfactant layer. The liposomes described in Lanza contain oil in the cores, not just fluorocarbon, which would solubilize many drugs. As the teachings of Lanza must inevitably and consistently lead to the claimed result in order to anticipate, the requirements for inherent anticipation are clearly not met.

The Rejection of All Claims as Anticipated By or Obvious Over Unger, US 2001/0018072

Applicants are grateful for the apparent recognition at the interview that the rejection over Unger is in error. However, to complete the record, the following response is provided:

As to the anticipation aspect of this rejection, it may be useful, once again, to consider the law on inherent anticipation. What is found to be anticipated must be the necessary and inevitable result of what is taught in the art. '072 Can only be said to teach that anything is possible. A wide variety of locations of any active ingredient is postulated. The disclosure of '072 appears to be nothing more than an assembly of boilerplate disclosure intended to cover every possible configuration, even though the claims are clearly directed to a solid porous matrix comprising random aggregates of a polysorbate surfactant in a therapeutic. It is difficult for applicants to see how '072 teaches liquid perfluorocarbon cores surrounded by lipid/surfactant layers in which a drug inevitably as required by anticipation, resides exclusively in the lipid/surfactant layer.

The body of the rejection appears to reinforce this. As noted, the vesicles (which appear to have nothing to do with what is actually being claimed in '072) may comprise a lipid/surfactant layer and a void (citing paragraph 33). But applicants' particles do not have a lipid/surfactant layer and a void; they have a lipid/surfactant layer and a perfluorocarbon core. The paragraphs cited by the Office (0121 and 0122) simply describe a variety of constructs which might or might not be relevant to whatever is being taught in '072. Taken as a whole, '072 simply discloses that a wide variety of formulations is possible and hardly suggests to the skilled artisan that perfluorocarbon liquid nanoparticles be prepared where a drug resides exclusively in the lipid/surfactant coating.

Indeed, the assertion by the Office that '072 provides motivation for one of ordinary skill in the art to formulate a tissue/organ targeting microparticle-based composition comprising a fluorocarbon core (or void, liquid or gas) coated with a lipid layer and coupled to the targeting ligand where the drug is incorporated into this lipid layer, simply is not found in '072. Applicants find no place in '072 where it teaches "the benefits of formulating a ligand-targeting vesicle/lipid composition wherein an active agent can be incorporated in the lipid portion of the composition." On the contrary, '072 clearly teaches that a wide variety of delivery compositions that might be useful and, judging by what is claimed, if it points to anything, it is to a solid porous matrix of polysorbate and a drug, very different from what applicants are claiming.

Applicants do not believe that the Office has responded to these arguments that were, indeed, made previously. Rather, the Office in its response points out that the phrase "comprising" does not exclude the presence of solids (which it may not, although clearly a liquid fluorocarbon is required) and asserts that '072 teaches that since the biological agent can migrate from the inner or outer surface of one microparticle to the surface of another microparticle it is present in the lipid layer. This does not rise to the level of teaching exclusive presence of the drug in the lipid/surfactant.

The Office asserts that the submitted declaration has not shown that the drug is only present in the lipid layer. The declaration does not provide experimental results to this fact. However, that is not the issue. The Office has not questioned the adequacy of description and the enabling nature of the specification. If there is some doubt that the specification teaches how to place the drugs exclusively in the lipid/surfactant layer, 35 U.S.C. § 112, should be the basis for rejection, not rejection over the art.

In summary, '072 appears to suggest nothing more than that there is a wide variety of drug delivery preparations available, and from its claims, it appears that what is "suggested" out of all that is vastly different from what even Unger is claiming.

Conclusion

Applicants again express their appreciation to Examiners Woodward and Barham for the thoughtful interview conducted on 19 July. It is believed that the present amendment and response place the claims in a position for allowance.

In view of the failure of the prior art to teach or suggest the claimed invention, claims 71-79 and 82-93 may be passed to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532512000401.

Dated: August 20, 2007

Respectfully submitted,

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